Cdk2ap2 is a Novel Regulator for Self-Renewal of Murine Embryonic Stem Cells.

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Public Summary:
We have started to explore the function of CDK2AP2, a sibling molecule of CDK2AP1, during mammalian development. Mouse embryonic stem cells with a significant reduction of Cdk2ap2 expression show a spontaneous exit from self-renewal. Analyses of expression of pluripotent markers showed significant changes with an increase in differentiation specific genes. These data suggest that Cdk2ap2 is required to sustain the self-renewal capacity of mESCs. This was further supported by an expression analysis during differentiation of wild type mESCs, wherein expression of Cdk2ap2 was significantly downregulated at day 2 of differentiation when mESCs exit self-renewal and commit to the various germ lineages. Experiments to identify the differentiation potential of the knockout mESCs showed that Cdk2ap2 knockout mESCs failed to undergo proper differentiation in vitro and in vivo. These data support a role for the Cdk2ap2 gene in maintaining cell survival during terminal differentiation of mESCs. Although the detailed mechanism explaining the function of Cdk2ap2 remains to be understood, the data presented here support a novel role for the Cdk2ap2 gene in regulating self-renewal of mESCs and survival of differentiating cells. It is speculated that Cdk2ap2 may be interacting with protein complexes similar to Cdk2ap1, but are having the opposite effect. Further studies need to be done to elucidate the exact mechanism of Cdk2ap2 function, especially in the context of how this mechanism works in relation to other Cdk2-associated proteins.

Scientific Abstract:
In this study we present data to support the role for Cdk2ap2 in regulating self-renewal of mouse embryonic stem cells (mESC) under permissive conditions, and cell survival during differentiation of the mESC into terminally differentiated cell types. To understand the function of Cdk2ap2 during early development we generated mESC with homozygous disruption of the endogenous Cdk2ap2 locus (Cdk2ap2tr/tr). The Cdk2ap2tr/tr mESC, when grown in complete growth medium containing LIF, showed an early differentiation phenotype characterized by flattened colonies and a distinct intercellular boundary. We also observed downregulation of Nanog and upregulation in markers of mesoderm and endoderm differentiation including, Brachyury (T), Afp, and S100a, when compared to Wt mESC. Cdk2ap2tr/tr mESC were able to form Embryoid Bodies (EBs) however those EBs were unhealthy and had an increased level of apoptosis. Furthermore, Cdk2ap2tr/tr mESC were unable to form teratomas in SCID mice. Cdk2ap2 under normal conditions has a biphasic expression suggesting regulatory roles in early vs. late stem cell differentiation. These data begin to add to our understanding of how Cdk2ap2 may be involved in the regulation of self-renewal of stem cells during early embryogenesis.